ANTIMICROBIAL PLASTICS

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Abstract of **WO 0053413 (A1)**

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(57) Abstract

Polyethylene Terephthalate or PET plastic bottles or containers are commonly used by the beverage and food industry. Multilayered bottles, with polyethylene inner layers are also used. Several other plastic materials are used in food, cosmetic and consumer and medical industry which become prone to contamination and biofilm formation by microorganisms. The current invention discloses a method of incorporating antimicrobial compositions in a plastic such as PET. Specifically, the current invention discloses a method of incorporating antimicrobial formulations and compositions as coatings inside bottles, preforms, capliners or processing containers that release the food preservatives slowly into the contacting beverage or food to prevent spoilage. A method of direct incorporation into the PET resin is also disclosed.

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ANTIMICROBIAL PLASTICS

This application claims the priority of U.S. Provisional Application No. 60/123,119, filed March 6, 1999, which is hereby incorporated by reference.

Field of the Invention

This invention is directed to antimicrobial plastics and methods for making same, and specifically directed to antimicrobial materials for use in food packaging and medical applications.

Background of the Invention

Citrus and other fruit juice processing operations present an important part of the food industry in the U.S and the world. Pasteurized single strength juices and frozen concentrates are two major types of products. These products are not free of microbiological spoilage problems. Yeast, molds, and lactic acid bacteria have been implicated in spoilage of fruit juices. Molds may be temporarily injured by minimal heat processing, making them difficult to detect with normal quality control procedures. However, such injury to the mold may be repaired if presented with the proper temperature and moisture conditions. Although the low pH and high sugar content of most juice concentrates create a restrictive milieu for the growth of most microorganisms, xerotolerant yeast can still grow to unacceptable levels under these conditions.

The main purpose of packaging is to protect food from microbial and chemical contamination, oxygen, water vapor and light. The type of packaging used therefore serves an important role in determining the shelf life of the food. Packaging with antimicrobial effects, so-called "active packaging," does more than simply provide a barrier to outside influences. It can control and even react to events taking place inside and outside the packaging. Thus, antimicrobial packaging perform two very important functions. First, such packaging resists surface contamination by air-borne and other types of microbes which may settle on the surface of packaging materials. Second, it actively preserves the freshness of the packaged item by virtue of leaching small amounts of the antimicrobial agent onto, or in the case of a liquid item, into the item itself.

The addition of preservatives to fruit juices and fruit juice beverages is common. Although, the need for preservatives is less for single-serving size cans or bottles, the shelf life of a product becomes an issue when large quantities such as a 4-liter bottles needs to be stored for several weeks. The shelf life of such products that contain no preservatives run the risk of showing signs of spoilage when stored at ambient temperatures. Occasionally a poor seal may also allow air borne microbes to enter the surface of the fruit juice. Spoilage is more rapid between 20C and 35C and normally slows down as temperature decreases.

Typically, preservatives such as sodium benzoate and parabenzoate are added in concentrations of 0.1% w/v directly to liquid fruit juices and fruit juice beverages stored in plastic or glass bottles. While the need for the antimicrobial agent to preserve freshness is well-accepted, it is much more desirable to add the smallest amount of preservatives as possible, and where possible, to the packaging material and not the perishable food item itself. It is also desired to be able to decrease the amount of preservatives required without requiring drastic and costly changes to common packaging methods, namely plastic bottles.

The present invention describes alternatives to the traditional practice of adding preservatives directly to foods. This invention teaches coating the surfaces of plastic containers with antimicrobial additives. Some coatings that adhere very well to the surfaces of commonly employed plastic bottles and which release the additives slowly with time into the contacting media are described. This invention also teaches directly incorporating one or more antimicrobial additives into the raw material polymer used to create the packaging. Both methods present useful and long-needed solutions for improving the packaging of materials used for food packaging, and for decreasing the amount of preservatives needed to inhibit microbial growth. These methods may also be readily used in many other applications, such as the fabrication of medical devices such as catheters or stents.

The antimicrobial compositions that can be directly incorporated in plastics and the methods are also described. Such treatments provide surfaces that resist microbial contamination and the incidental leachates serve to control microbial growth in the contacting media as well.

Summary of the Invention

Applicant has found that a significantly smaller amount of antimicrobial agents is required to preserve the freshness of a food product when the agents are added to the packaging material and not the product itself.

In one aspect, this invention provides antimicrobial coatings for application on surfaces of plastic bottles, and other containers based on a polymeric substrate that eliminate the need to add preservatives directly into the food product.

In one embodiment of this aspect, the invention provides for coatings comprising various polymeric coating vehicles which adheres well to a polymeric substrate, and one or more food grade preservatives, which when applied to the polymeric substrate, becomes integrated into the structure of the substrate.

In another embodiment of this aspect, this invention provides compositions of antimicrobial inner coatings to packaging containers, such as polyethylene terephthalate (PET) such that microbial survival is prevented under all conditions starting from the initial filling of the container with food or other items through the extent of its storage life.

In another embodiment of this aspect, this invention provides solvent-based coating systems that are antimicrobial and adhere well to PET and other polymeric substrates, and are formulated with FDA approved food preservatives.

In another aspect, the invention provides for antimicrobial compositions that may be directly incorporated into polymeric resin, that results in a finished container with antimicrobial activity, and methods for making same.

In one embodiment of this aspect, the invention provides for plastic containers that discourage microbial growth during storage of perishable and other items, and releases small quantities of various antimicrobial reagents into the item in a time dependent manner.

These and other features and objects of the present invention will be more fully understood in the following detailed description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The antimicrobial activity in plastics is dependent on the molecular diffusion of the biocide and its slow release into the juice. Polymers that exhibit a low glass transition temperature usually allow this diffusion to occur fast enough to provide adequate protection against the proliferation of microbes. Thus, when an additive is added to these polymers, it diffuses through the thickness of the substrate polymer and "blooms" to the surface, where it comes into contact with the food medium. But in crystalline polymers such as polyethylene terephthalate (PET), one of the most common materials used for packaging beverages, the diffusion is somewhat limited. Furthermore, current PET containers used for juice packing are quite thin and substance applied to the container needs to provide a high area of contact with the juice in order to be effective.

Through extensive experimentation, Applicant has determined that a satisfactory level of molecular diffusion of antimicrobial agents can be achieved using one of two methods. In the first method, a composition of antimicrobial agents having desired properties is incorporated into a coating which is then applied to at least the inner surface of the container, either in a pre-formed state (prior to stretch blow molding) or in the finished state. Application of the coating to the finished packaging article is ideal when the antimicrobial articles are temperature-sensitive, or otherwise not suited for treatment with high temperatures. Such additive candidates include sorbates, dicarbonic esters, sulfites, carbonates, Nisin, biphenyls, Nystatin, benzoic acid, salicylic acid, parabens, and phenols. For these compounds that are stable at a temperature of about 100-120C, the coating containing these additives may be applied to a pre-form of the polymeric resin, which is then heated to about 100-120C and stretch blow molded to its final dimensional specifications.

In a second method, the antimicrobial ingredients are directly blended into the polymeric resin that is then melted at relatively higher temperatures to create the finished plastic container. This direct blending typically takes place at or above the melting point of the polymeric resin, e.g. about 530F for PET resin. Such high temperature direct blending is suitable for additives that do not generally decompose at these temperatures, such as benzoates, propionates, nanosilver, thiabendazole, silver

salicylates, silver fluorides, copper carbonates, nanocopper, silver powder, or phosphates.

Applicant has determined that in order to facilitate the coating of polymeric substrates with antimicrobial preservatives through plastic, two different types of solvent-based coating vehicles may be used. The first is a biodegradable polyester, aka biopolyester (biopolyethylene terephthalate, or BPET) sold by Eastman Chemicals, Kings Port, Tennessee, EASTSTAR Bio 14766™ which Applicant has determined is a suitable material to incorporate the various food preservatives which are compounds or combinations of compounds approved by the U.S. Food and Drug Administration as well as by regulatory agencies of various European countries. A second suitable solvent-based coating vehicle is a polyester resin solution sold by Morton Adhesives and Chemical Specialties, by the trade name ADCOTE 40-3. Applicant has determined that this polyester resin is also suitable for use as a carrier for coating plastic bottles with food preservatives.

Applicant has found that when a coating vehicle such as BPET or polyester resin is combined with one or more preservatives and applied to a finished container, acceptable levels of biocidal activity are achieved. Furthermore, Applicant has determined that effective levels of biocidal activity may also be achieved when the preservative/coating vehicle is applied to a preform bottle prior to stretch blow molding, and also when directly incorporated into the polymeric resin raw material prior to pre-forming and stretch blow molding. In particular, direct blending of certain food preservatives with PET resin were effective when followed by fabrication of pressed films from about 500F to 550F.

PET and various other polymeric materials are commonly used in the food and beverage packaging industry. Typically, pellets of PET or other polymeric material is melted, typically at a temperature of about 530F for PET, in single or multi-layers, comprising the same or difference polymeric materials, and injection-molded into a pre-form. As will be appreciated by one of ordinary skill in the art, resin pre-forms can be created using standard equipment such as that sold by Husky of Toronto, Canada. The pre-form is then stretched blow molded at a lower temperature, typically about 100-150C with hot air to expand and stretch the pre-form to its desired

dimensional specifications, again using standard equipment such as blow-molding equipment sold by Sidel of France. Typically, multi-layer PET-based bottles comprise a barrier layer such as nylon material, interspersed among virgin layers of PET which form the outer surfaces.

As understood by one of ordinary skill in the art, various preservatives may be employed. For instance, in addition to the preservatives identified in the following Examples, sulfite salts such as calcium sulfite and sodium sulfite are also possible candidates for direct incorporation into the polymeric resin used to create the packaging material. These preservatives will diffuse to the surface of the container in contact with food and are hydrolyzed to produce sulfur dioxide which is an excellent inhibitor of mold and yeast.

Such compounds which hydrolyze and release sulfur dioxide or carbon dioxide may be incorporated in the polymeric substrate such as PET, by a direct addition into the PET resin prior to melting or as a coating on a pre-form or stretch-molded PET container depending on their thermal stability. As appreciated by one of ordinary skill in the art, carbon dioxide releasing chemicals may be carbonates of Ca, Mg or other non-toxic metals or dicarbonic acid esters. For instance, dimethyl esters (Sigma) and diethyl esters are well known to release carbon dioxide and ethanol at low levels.

Other additives may comprise copper salts such as carbonates or chlorides or other non-toxic anions. In the presence of juices that contain ascorbic acid, the divalent copper ions react with ascorbic acid producing hydrogen peroxide and transient -OH radicals which could prove to be of extreme value in biocidal action. The -OH radicals and hydrogen peroxide have broad spectrum biocidal effects.

EXAMPLE 1

For the initial evaluations, clean, monolayer PET bottles of 16 ounce in size were dried in an oven for 3 hours at about 80C. The Eastman biopolyester resin (BPET) was dissolved in tetrahydrofuran (THF) to give a concentration of 10% w/v. Exactly 3.0 grams of benzoic acid or 2.0 gms of ethyl paraben or propyl paraben with or without silver powder 0.1%. (Sigma - Aldrich, Missouri, Cerac corporation) was added to 100 ml of the 10% w/v BPET solution. Clear solutions were obtained. The

dried bottles were then each coated with 10 ml of this formulation with and without the additives, by rotating the bottles to coat the sides. After drying overnight at ambient temperature, the coated bottles were subjected to a temperature of 150C for 15 minutes to mimic the temperature conditions during the stretch blow molding of the PET pre-forms.

The bottles were then capped by caps subjected to the same temperature and carefully wrapped in aluminum foil heated to the same temperature. For coating with the Morton's ADCOTE material which comes as a dispersion of 65% solids in MEK (methyl ethyl ketone), the following procedure was used. The ADCOTE dispersion is diluted about 3 times, and a 3% benzoic acid solution was prepared in this dispersion. Each dried bottle was coated with 10 ml of this dispersion with and without the preservative, benzoic acid. After 24 hours, the bottles were subjected to a heat treatment for 15 minutes at 150C.

Other formulations include 2% ethyl paraben, 2% propyl paraben (Sigma Chemical) plus 0.1% silver powder having an average particle size 1 micron (Cerac Corporation). Each bottle was coated with 10 ml of these formulation in triplicate. The bottle codes and the formulations are shown below.

Table I. Maximum Concentration of Antimicrobials in Apple Juice of Coated Bottles

Bottle code	Polymer	Additive	Amount of Polymer + Additive/ Bottle	Maximum Concentration in 300ml of juice
"A"	Biopolyester (BPET) 10% in THF	3% Benzoic acid	10mL	1000ppm or 0.1%
"B"	BPET	1.5% Benzoic acid	10 ml	500ppm (0.05%)
"BMS"	BPET	2% Propyl paraben + 0.1 % silver powder	10ml	660 ppm (0.06%)
" AD"	ADCOTE 1:1 with	3% Benzoic acid	10 ml	1000ppm (0.1%)

	methyl ethyl ketone			
"D"	BPET	2% Ethyl paraben	10 ml	660 PPM (0.06%)

BPET=biopolyester

THF=tetrahydrofuran

EXAMPLE 2

Microbiological Protocols

Two cultures, a mold and a yeast (*P. roquefortii and Zygosaccharomyces Bacilli)* were received from a commercial juice processing plant. The *P. Roquefortii* species was grown in malt extract broth (MEB) and then maintained on malt extract agar plates. The yeast species was grown in potato dextrose broth (PDB) and maintained on potato dextrose agar (PDA) plates. All incubations were carried out at 25C in an incubator. The media used for the microbiological tests was pasteurized apple juice commercially available off the store shelf. The sterility of this juice medium was often checked by assaying the juice.

Yeast

A potato dextrose agar plate containing Z. *Bacilli*, an yeast was used. A loopful of yeast cells was inoculated into 5ml of sterile PBD (Difco) at 25C for 48hrs. The optical density (OD) of the juice suspension was measured after gently vortexing at 550 nm against a PDB blank. OD was determined to be approximately 1.048. The mathematical relationship that the theoretical OD of 0.021 contains 10^6CFU/mL yeast cells (0.021X 1ml/observed OD = ml of culture to be diluted) was used, with apple juice as the diluent.

Then, 10 microliters of the above diluted medium was pipetted into 990 microliters of apple juice, and vortexed, resulting in a concentration of 10^4cfu/mL. One-hundred microliters of this mixture contains 1000 cells, and bottles were inoculated using appropriate dilutions. Plate counts for the inoculum were taken.

Mold

An malt extract agar plate containing the fresh Penicillium mold colonies was used. To 5mL of apple juice, a loopful of the mold from a fresh plate was added. The

OD of the juice suspension was measured at 550nm. It was approximately 0.116. The mathematical relationship that 0.008 OD contains 10^5cfu/mL of mold cells was used to dilute the culture (0.008X1mL/ observed OD = ml of culture to be diluted to 1mL). Then, 100 microliters of diluted cell medium (10^5cfu/mL) was pipetted into 900 microliters of apple juice, and vortexed, creating a medium with a cell concentration of 10^4cfu/mL. This medium or appropriate dilutions were used to inoculate bottles, with a 100 microliters/bottle. The medium was diluted and plated appropriately to get plate counts for the inoculum.

Challenging with Yeast and Mold

The bottles to be inoculated, as well as the set of control bottles were filled with commercially available filtered apple juice at 170F (whose sterility was confirmed with repeated tests) and then allowed to cool to room temperature. Each bottle (except the control bottles) were inoculated with about 100 cells of the Penicillium mold or with *Zygosaccharamyces Bacilli* yeast species. The inoculated bottles were gently swirled and left undisturbed in an incubator at 25C. Over the course of three weeks, the inoculated bottles were visually inspected for the appearance of mold growth on the surfaces of the apple juice samples. For the yeast, the bottles were gently removed and held against bright light to check for turbidity of the juice. The results of the visual inspection tests for two sets of tests are given below.

Table II. Visual Inspection of Inoculated Apple Juice for Mold/Yeast Growth

Test A:

Days	Control (mold)	Sample (mold)	Control (yeast)	Sample (yeast)
48hrs	Growth	None	Growth	None
1 week	"	"	"	"
2 weeks	"	"	"	Slight cloudiness
3 weeks	"	"	" White residue	White residue at the bottom

Test B:

Days	Control (mold)	Sample (mold)	Control(yeast)	Sample (yeast)
48hrs	Growth.	None	Growth	None
1 week	"	"	"	None
2 weeks	"	"	"	None
3 weeks	"	"	" White residue	None

At each time point as shown below, the juice media was assayed by spreading 100 microliters on a PDA plate for the yeast and MEA plate for the mold.

Tables III, IV, and V show microbiological challenge results of the juice contacting the various coated and uncoated bottles. Table III shows the use of a coating comprising benzoic acid and BPET. The benzoic acid, when added to the coating at a concentration of 3.0% (all of the "A" samples), was effective at inhibiting the growth of yeast. Assuming that all of the benzoic acid in the coating dissolved instantly and diffused into the apple juice, this coating would provide 0.1% w/v concentration of benzoic acid in the juice. It is, however, possible that the benzoic acid in the coating did not come into contact with the juice at once but slowly partitioned between the juice and the coating. Also, the acidity of the juice (pH of about 3) decreases the solubility considerably (compared to the solubility of benzoic acid in water of 0.34g/100gm of water). The "B" samples contain 1.5% benzoic acid in the coating. The maximum concentration of benzoic acid provided in the apple juice is 0.05% benzoic acid.

Table III. Growth of Yeast in Antimicrobial Coated Apple Juice Bottles

	Incubation Time				
Bottle Identification	48 hours	5 days	10 days	15 days	25 days
Control – 1	No visible growth	1.8×10^7 cfu/ml	1.5×10^7 cfu/ml	4.8×10^6 cfu/ml	Confluent
Control – 2	No visible growth	1.1×10^7 cfu/ml	1.4×10^7 cfu/ml	6.4×10^6 cfu/ml	Confluent
Control – 3	No visible	5.9×10^6	1.4×10^7	5.3×10^6	Confluent

	growth	cfu/ml	cfu/ml	cfu/ml	
A-1	0*	0	0	0	0
A-2	0	0	0	0	0
A-3	0	0	0	0	0
B-1	10 cfu/ml	0	0	0	0
B-2	0	1.8×10^3 cfu/ml	8.0×10^6 cfu/ml	9.5×10^5 cfu/ml	1.8×10^6 cfu/ml
B-3	10 cfu/ml	1.4×10^2 cfu/ml	8.3×10^6 cfu/ml	3.4×10^6 cfu/ml	1.0×10^6 cfu/ml

Initial challenge inoculation (Time = 0 hours incubation) was 4.9×10^2
cfu = colony forming units
* = Zero indicates no growth was observed. This method has a detection limit of <10 cfu/ml.

Table IV shows the ability of benzoic acid to inhibit the growth of mold when used as a coating in conjunction with BPET. The same coating concentrations were utilized as in Table III.

Table IV. Growth of Mold in Antimicrobial Coated Apple Juice Bottles

	Incubation Time				
Bottle Identification	48 hours	5 days	10 days	15 days	25 days
Control-4	No visible growth	Surface growth	Surface growth	Surface growth	Surface growth
Control-5	No visible growth	No visible growth	Bottom flock	Bottom flock	Bottom flock
Control-6	No visible growth	Surface growth	Surface growth	Surface growth	Surface growth
A-4	10 cfu/ml	0	0	0	0
A-5	0*	0	0	0	0
A-6	0	0	0	0	0
B-4	0	0	0	0	10 cfu/ml
B-5	0	0	0	0	0
B-6	0	0	0	0	0

Initial challenge inoculation (Time = 0 hours incubation) was 1.2×10^3 cfu/ml
cfu = colony forming units
* = Zero indicates no growth was observed. This method has a detection limit of <10 cfu/ml.

Table V shows the use of benzoic acid to inhibit the growth of yeast in plastic bottles coated with a combination of benzoic acid and either BPET or ADCOTE polyester resin. The

bottles labeled AD contained ADCOTE-based coatings, while bottles labeled BMS and D contained BPET based coatings.

Table V. Growth of Yeast in Antimicrobial Coated Apple Juice Bottles

Bottle Identification	Incubation Time		
	4 days	7 days	11 days
Control	8.2 x 10^6 cfu/ml	3.6 x 10^7 cfu/ml	3.7 x 10^7 cfu/ml
Control-BPET	8.2 x 10^6 cfu/ml	5.0 x 10^7 cfu/ml	3.4 x 10^7 cfu/ml
AD-1	0*	0	0
AD-2	1.5 x 10^5 cfu/ml	7.4 x 10^6 cfu/ml	1.2 x 10^7 cfu/ml
AD-3	1.5 x 10^5 cfu/ml	8.9 x 10^6 cfu/ml	1.1 x 10^7 cfu/ml
BMS-1	0	0	0
BMS-2	0	0	0
BMS-3	0	0	0
D-1	0	1.8 x 10^2 cfu/ml	7.0 x 10^3 cfu/ml
D-2	3.1 x 10^3 cfu/ml	3.7 x 10^5 cfu/ml	107 x 10^7 cfu/ml
D-3	4.5 x 10^3 cfu/ml	4.6 x 10^4 cfu/ml	6.7 x 10^6 cfu/ml

Initial challenge inoculation (Time = 0 hours incubation) was 76 cfu/300mL
cfu = colony forming units
* = Zero indicates no growth was observed. This method has a detection limit of <10 cfu/ml.

Tables VI and VII show the release of various preservatives from BPET-based coating as a function of time.

Table VI. Concentrations of Antimicrobials in Apple Juice of Coated Bottles as a Function of Time

Bottle ID	Identity of the antimicrobial	48 hrs	7 days	15 days
A	Benzoic acid	846 ppm (0.08%)	966 ppm (0.096%)	1000 ppm (0.1%)
B	Benzoic acid	330, 318, and 344 ppm (0.035%)	515, 475, and 600 ppm (0.05-0.06%)	

BPET was used as the coating vehicle.

Table VII. Concentrations of Antimicrobials in Apple Juice of Coated Bottles as a Function of Time

Bottle ID	Identity of the antimicrobial	4 days	7 days	11 days
AD	Benzoic acid	380 ppm	350ppm	674ppm (0.067%)
D	Ethyl paraben	399 ppm (0.04%)	357ppm	366ppm
BMS	Propyl paraben	233 ppm (0.02%)	241	247
BMS	Silver	Less than 1 ppm	Less than 1 ppm	Less than 1 ppm

AD=ADCOTE as coating vehicle.
D and BMS=BPET as coating vehicle.

The results from Tables VI and VII indicate that when the polyester resin formulation sold by Morton Adhesives under the trademark ADCOTE 40-3™ is used as the solvent-based coating vehicle, the antimicrobial ingredients are released rather slowly. In contrast, depending on the active ingredient, when the biodegradable polyester (BPET) based formulation sold by Eastman Chemicals under the name EASTSTAR Bio 14766 is used as the solvent-based coating vehicle, the release of the coating into the juice was either relatively fast (as in benzoic acid), or slow (as in propyl paraben and ethyl paraben).

The surprising effect of extremely small amounts of silver and phenolic compounds such as parabenzoic esters is seen in the effectiveness of such coatings. The release of propyl paraben from the biopolyester coating was slow and maintained at levels of 240ppm and was still effective. In preliminary test results, the combination of silver and phenolic compounds such as paraben was found to be surprisingly

effective in preventing yeast and mold growth is reported. Such combinations with silver and other preservatives were found to be effective against *E. coli*.

EXAMPLE 4

This example tests the efficacy of antimicrobials that are directly blended with PET resins, prior to melt pressing (or injection molding) at high temperatures. Typically, plastic bottles are fabricated in two stages. In the first stage, the plastic resin, such as PET, is heated to a temperature of about 550F and melt pressed to create a pre-form. In the second stage, the pre-form is stretch blow molded to its final specifications at about 150C (about 330F).

It is widely known that at high temperatures, at around 500F or greater, certain antimicrobial agents will decompose or degrade. Thus, the antimicrobial activity of certain additives that were directly incorporated into PET plastic prior to processing at high temperatures is described in this example. Polyethylene terephthalate (PET), in pellet form, was purchased from Aldrich Chemical and used after drying at 110C in a vacuum oven. The additives, such as potassium benzoate, calcium propionate, or silver benzoate or citrate (1-5% by weight) were mixed with the PET pellets and melt pressed at 540F using a hydraulic press. Control PET films without the additive were also made under the same conditions. Small strips of 1cm by 3 cm were cut and used for the microbiological assays. As will be appreciated by one of skill in the art, based on Applicant's findings, direct blending using plastics other than PET, such as biopolyester resin blended with various preservatives, is within the scope of this invention.

PET melts at a high temperature close to 530F and crystallizes very slowly. These initial experiments focused upon the antimicrobial efficacy of additives blended at a very high temperature and not on achieving a desired level of polymer crystallization. Similarly, although the amount of additive added was carefully controlled, the uniform dispersion of the additive in the plastic was not. This caused some non-reproducibility of the results.

Table VII shows the efficacy of additive potassium benzoate that was directly added to PET resin prior to melting in inhibiting microbial growth. The release rate of the additive as well as the dispersion of the additive caused some variations. It is clear

from the preliminary results that the potassium benzoate is very effective in completely inhibiting the mold and yeast species. In all experiments, both the control blanks and the control disks showed turbidity (indicating growth of microbial colonies) after 48 hours of incubation at 25C. The sample disks inhibited growth completely, reducing the cell numbers to zero, as evidenced by the plate counts.

Microbiology Test Protocol

Typically, 3 sterile strips were placed in 3 tubes containing 3 ml of sterile apple juice from a commercial bottle, and challenged at two levels 1) 1000cells /3mL (approximately 300cells/mL) and 100cells /3mL (30 cells/ml). Each tube contained one of the following:

a) additive-incorporated PET strip,

b) control PET strip;

c) no PET strip (control blank containing juice only).

Duplicate samples of the strips were also placed in tubes of sterile apple juice and inoculated with 10uL of 10^5 cfu/ml or 10uL of 10^4cfu/mL of the yeast species. The mold inoculation was conducted using the same procedure, in another set of tubes containing the samples, controls, and control blanks. Both visual and plate counts were monitored for all the test tubes and carefully recorded.

Table VII: Microbiological Challenge Results on Antimicrobial Incorporated PET Films

Start Date	Juice Added				Growth on each day #(N,L,M,H), days time from when apple juice was added								
Start Date	Juice Added	Additive	Bottle Type	Initial Cells	5								
12/30/99	12/30/99	S.A.	Control	10 2b	H								
071-085	a-d	S.A	Control	10 2b	H								
		---	Control	10 2b	H								
		Zn,Cu	Control	10 2b	H								
		Zn,Cu	Control	10 2b	H								
		---	Control	10 2b	L								
					8								
12/29/00	12/29/00	---	Control	1 2b	H								
071-083	a-d	---	Control	1 2b	H								
		---	ICET 1	1 2b	M								
		---	ICET 1	1 2b	H								
					3	4	10	12					
1/14/00	1/14/00	---	Control PET	50 P.R.	N	L	M	M					
071-099	a,b,e,f	---	Control PET	50 P.R.	L	L	H	H					
		---	ICET 1	50 P.R.	N	N	M	M					
		---	ICET 1	50 P.R.	N	N	N	L					
					4	6	7						
1/14/00	1/20/00	---	Control PET	50 P.R.	M	H	H						
071-099	c,d,g,h	---	Control PET	50 P.R.	L	M	M						
		---	ICET 1	50 P.R.	L	L	M						
		---	ICET 1	50 P.R.	L	L	M						
					1	3	7	9					
1/17/00	1/17/00	Cu,Fe	Control PET	4 P.R.	N	H							
062-058	a-i	F	Control PET	4 P.R.	N	M							
		AgSal	Control PET	4 P.R.	N	N	N	N					
		AgSal,F, Cu,Fe	Control PET	4 P.R.	N	L							
		Cu,6P	Control PET	4 P.R.	N	M							
		---	Control PET	4 P.R.	N	M	H	H					

N=No growth
L=Low growth
M=Medium growth
H=High growth

Zb=Z. Bacilli
AgSal=Silver salicylate

Table VII continued: Microbiological Challenge Results on Antimicrobial Incorporated PET Films

					4	6	11	13	15	18	20	25	27
1/20/00	1/20/00	---	Control PET	57 P.R.	L	N	L	L	L	L	L	L	L
062-065	(at 82C)	---	Control PET	57 P.R.	N	N	L	L	L	L	L	L	L
a-d		---	ICET 1	57 P.R.	N	N	L	L	L	L	L	L	L
		---	ICET 1	57 P.R.	L	L	M	M	M	M	M	M	M
					3	5	10	12	14	17	19	24	26
1/21/00	1/21/00	AgSal	Glass Tube	5 P.R.	N	N	N	N	L	L	M	M	M
062-069	e-j	AgSal	Glass Tube	5 P.R.	N	N	L	L	L	M	M	M	H
		---	Glass Tube	5 P.R.	L	L	M	M	M	H	H	H	H
		---	Glass Tube	5 P.R.	L	L	M	M	M	H	H	H	H
		---	Glass Tube	0	N	N	L	L	L	L	L	L	L
		---	Glass Tube	0	N	L	M	M	M	M	M	M	M
					4	6	8	11	13	18	20		
1/27/00	1/27/00	---	Glass Tube	18 P.R.	L	M	M	M	M	M	M		
062-076	g-n	---	Glass Tube	18 P.R.	L	M	M	M	M	M	M		
		AgSal 2ppm	Glass Tube	18 P.R.	N	N	N	N	N	N	N		
		Ag Sal 2ppm	Glass Tube	18 P.R.	N	N	N	N	N	N	N		
		AgSal 1ppm	Glass Tube	18 P.R.	N	N	N	N	N	N	N		
		AgSal 1ppm	Glass Tube	18 P.R.	N	N	N	N	N	N	N		
		---	Glass Tube	0	N	N	N	N	N	N	N		
		---	Glass Tube	0	N	N	N	N	N	N	N		
					2	11	13						
2/5/00	2/5/00	---	Control PET	Zb	N	N	N						
Helina		---	Control PET	Zb	N								
		---	ICET 1	Zb	N	N							
		---	ICET 1	Zb	N	M							
		---	ICET 2	Zb	N	N							
		---	ICET 2	Zb	N	N							

EXAMPLE 5

Another embodiment of this invention discloses a polyurethane coating using a pre-polymer HYPOL™ (trademark of Dow Chemicals) blended with various preservative formulations and nanosilver. The nanophase silver (Nanophase Technologies, Illinois) is an high surface area material with particle sizes typically ranging from 2 to 20 nanometers. As used herein, the term nanosilver refers to silver particles with a size smaller than one micron. Such dimensions are very close to molecular dimensions and several advantages can be realized by this invention. The blending of the silver with the PET resin, and the high surface area of nanosilver results in a high level of activity of silver at low loading. Nanotechnology is a nascent area and the uses of nanosilver as a biocide has distinct advantages, namely, greatly increased surface area of active silver per equivalent weight of silver having the same general particle geometry.

Nanoparticles of silver were prepared having approximate dimensions of 2 x 20 x 20 nanometers. (National Institute of Mat. Chem. Res., Tsukuba Ibaraki, Japan (1997)). These particles have volumes of approximately 800 cubic nanometers and surface areas of 500-600 square nanometers or approximately 10^{34} square nanometers of surface area per milligram of silver. Because of the increased surface area, a smaller mass of silver is required to obtain greatly enhanced protection.

Applicant has determined that nanosilver in combination with other compounds, such as bismuth subsalicylate may prevent bacterial adhesion to plastic surfaces. A second, and surprising effect of nanosilver is its ability to accelerate the cure rate of certain polymers. Applicant found that the addition of nanosilver particles facilitated the curing of the polyurethane prepolymer, HYPOL™, in the presence of phenolic compounds.

A formulation was prepared by blending nanosilver with terpinol or thiabendazole. Normally, these phenolic compounds inhibit or block the curing of HYPOL™; however, the addition of nanosilver appears to overcome this problem.

EXAMPLE 6

A formulation combining different preservatives was prepared by blending 46g of thiabendazole (Sigma - Aldrich Chemical, Minnesota), 46g of sodium salicylate (Sigma - Aldrich) and 1g of nanosilver (as a suspension in alpha terpinol (Nanophase Technologies, Illinois) in a 2L base of a mineral oil compound, SPAN-85.™

Thiabendazole is an anti fungal compound fruit that is normally sprayed on citrus and other fruits. Residuals of this compound are found in various fruit juices , milk and meat. Thiabendazole is an excellent candidate for direct addition to high melting plastics such as PET due to its high melting point (about 305C) , which allows the compound to survive temperatures as high as 550F for PET bottle processing without decomposing.

The formulation was then metered in during the processing of the PET bottles using standard plastic bottle manufacturing equipment (Husky, Inc., Toronto, Canada) (Continental PET Technologies, New Hampshire). Pre-forms were made and then finished by stretch blow molding. No special processing changes were made and no problems were reported by the bottle manufacturer. The additive incorporated plastic PET bottles were then evaluated for their biocidal properties and also analyzed for the actual additive concentrations in the plastic and the contacting juice.

In a second test, the biocidal properties of a salicylic acid based composition was tested as well. A blend of 100g of salicylic acid (Sigma - Aldrich) and 23 g of thiabendazole was added to a base of 2L of SPAN-85. This blend was added to PET resins, and the resultant mixture was processed into a bottle by first pre-forming at a higher temperature followed by and stretch blow molding to final bottle specifications and then hot-filling heated apple juice at a lower temperature (170F). As understood by one or ordinary skill in the art, the apple juice may be added in a heated, cooled, or chilled state.

A silvered-form of salicylate, silver salicylate, was also tested by blending, silver salicylate, 25g, with SPAN-85™ mineral oil as described above. In a series of experiments, 0.5 ppm, 1 ppm, and 2 ppm of silver salicylate was introduced into 500 ml of apple juice containing bottles followed by the inoculation of a mold or yeast

species. Control bottles contained no added silver salicylate but contained the same number of organisms as the test bottles. On incubation for four weeks, the silver salicylate treated samples did not show any growth while heavy growth was noticed in the controls after only 4or 5 days.

The concentrations of various additives in the three different sections of the PET bottle (top, middle, bottom) and in the contacting juice were analyzed immediately upon juice contact with the treated-PET bottles and after two weeks of contact time. Table VIII provides the results of these tests, were available.

Table VIII. Chemical analysis of the PET bottle direct blended with silver, thiabendazole, and salicylate material and the contacting juices

Direct Blending of Additives into PET Bottle	Silver in the Plastic	Silver in the contacting juice	Thiabendazole in plastic	Thiabendazole in juice	Salicylate in plastic	Salicylate in juice
Prepared according to Example 6	Top: 0.87ppm	at t=0: <1ppb at t=2 weeks: <1ppb.	Top: 92ppb	at t=0 35ppb at t=2 weeks: 53ppb	N/A	N/A
	Middle: 0.82ppm		Middle: 82ppb		N/A	N/A
	Bottom: 0.86ppm		Botttom: 120ppb		N/A	N/A

EXAMPLE 7

This example describes a coating composition that could be useful for a broad spectrum of applications especially for catheters, stents or for any biomaterial susceptible to microbial contamination or infection.

A coating formulation was made as follows: 10g of HYPOL 5000™(Dow Chemical), 1g of titanium oxide (Degussa), 50mg of nanosilver (Nanophase Technologies), 1g of paraben (e.g. butyl) (Sigma Company), and 0.2 g bismuth subsalicylate (Alfa -Aesar, MA).

The HYPOL™ was mixed with the above ingredients diluted to about 20ml . This was then coated on a TECOFLEX™ EG 80A (Thermedics , MA) tubing by a dip coating method and dried overnight. Surprisingly the coating cured rapidly overnight. This result was surprising as phenolic compounds such as the parabens typically inhibit the curing process of isocyanates. It is one theory that the activity of the nanosilver in the compound overcame the inhibition.

The 2" coated tubes and controls were exposed to 10^8 cfu/ml of *S. aureus* and *E. coli* (American Type Culture Collection) for 3 hours, followed by washing and incubation in a growth medium of phosphate-buffered solution (PBS) and 10% BHIB (Brain-Heart Infusion Broth), a very rich growth medium.

The control samples allowed for the adhesion and the survival of the bacteria on the HYPOL™ substrate, as evidenced by visible growth in 1 day. The coated tubes resisted the bacterial adhesion and inhibited growth for up to 15 days.

The various technical and scientific terms used herein have meanings that are commonly understood by one of ordinary skill in the art to which the present invention pertains. As is apparent from the foregoing, a wide range of suitable materials and/or methods known to those of skill in the art can be utilized in carrying out the present invention; however, preferred materials and/or methods have been described. Materials, substrates, and the like to which reference is made in the foregoing description and examples are obtainable from commercial sources, unless otherwise noted. Further, although the foregoing invention has been described in detail by way of illustration and example for purposes of clarity and understanding, these illustrations are merely illustrative and not limiting of the scope of the invention. Other embodiments, changes and modifications, including those obvious to persons skilled in the art, will be within the scope of the following claims.

What is claimed is:

1. An antimicrobial polymeric product comprising:

a polymeric carrier resin;

one or more food-grade preservatives; and

a polymeric substrate, wherein the polymeric carrier resin and the preservative(s) are combined and applied to at least one surface of the substrate.

2. An antimicrobial plastic comprising:

a coating vehicle comprising a polyester resin;

a combination of one or more antimicrobial agents; and

a plastic resin comprising polyester wherein the coating vehicle and the antimicrobial agents are combined with the plastic resin and subjected to a temperature at about or above the melting point of the plastic resin and molded to produce a plastic solid with antimicrobial properties.

3. The plastic of claim 2, wherein the plastic resin comprises polyethylene terephthalate with a melting point of about 530F.

4. The plastic of claim 2, wherein the antimicrobial agents comprise benzoates, propionates, nanosilver, thiabendazole, silver salicylates, silver fluorides, copper carbonates, nanocopper, silver powder, or phosphates.

5. The plastic of claim 2, wherein the antimicrobial agents comprises a combination of salicylic acid, nanosilver, and thiabendazole in a base of mineral oil

6. The product of claim 1, wherein the polymeric carrier resin comprises solvent-based biodegradable polyester, polyvinyl chloride, or polyurethane.

7. The product of claim 1, wherein the polymeric substrate comprises polyester.

8. The product of claim 1, wherein the polymeric substrate comprises polyalkylene terephthalate.

9. The product of claim 1, wherein the polymeric substrate is selected from the group consisting of polyethylene terephthalate and polybutylene terephthalate.

10. The product of claim 1, wherein the food-grade preservative(s) is selected from the group consisting of: benzoates, propionates, nanosilver, thiabendazole, silver salicylates, silver fluorides, copper carbonates, nanocopper, silver powder, phosphates,
sorbates, dicarbonic esters, sulfites, carbonates, Nisin, biphenyls, Nystatin, benzoic acid, salicylic acid, parabens, and phenols.

11. The product of claim 10, wherein the parabens comprise methylparaben, ethylparaben, propylparaben and butylparaben.

12. An antimicrobial coating for polyester containers used in food and cosmetic packaging including polyethylene terephthalate containers comprising a solvent-based polymeric resin and at least one antimicrobial agent which are combined and applied to at least one surface of the polyester container.

13. The coating of claim 12, wherein the antimicrobial agents are selected from the group consisting of benzoates, propionates, nanosilver, thiabendazole, silver salicylates, silver fluorides, copper carbonates, nanocopper, silver powder, phosphates,
sorbates, dicarbonic esters, sulfites, carbonates, Nisin, biphenyls, Nystatin, benzoic acid, salicylic acid, parabens, and phenols.

14. The coating of claim 12, wherein the solvent-based polymeric resin comprises polyester, polyvinyl chloride, or polyurethane.

15. A method of making an antimicrobial polymeric container comprising:

(1) combining at least one food-grade preservative and a solvent-based coating vehicle comprising polyester resin to produce an emulsion/dispersion of the coating vehicle and the preservative(s);

(2) providing a polymeric substrate of a desired structure; and

(3) treating the substrate with the dispersion/emulsion such that the dispersion/emulsion defines at least one inner surface of the product; and

(4) drying said solvent from said treated substrate to produce a solid coating of dispersion/emulsion on said substrate structure having antimicrobial properties.

16. A method of making a polymeric container with an antimicrobial property comprising:

(1) providing a polymeric substrate comprising polyester resin that has been pre-formed into a desired structure;

(2) treating the pre-formed structure with a coating of a combination of a polyester-based coating vehicle and one or more antimicrobial agents such that the coating defines at least one inner surface of the substrate; and

(3) stretch blow molding the pre-formed structure into a container structure, whereby the antimicrobial agent(s) is incorporated throughout a substantial portion of the inner surface of the container structure.

17. A method of making an antimicrobial polymeric package comprising:

(1) combining at least one food-grade antimicrobial agent with a polymeric resin;

(2) melting the combined resin and agent(s) to produce a treated resin compound;

(4) shaping said treated resin compound into a desired shape via injection molding; and

(5) stretch blow molding said shape into a desired package structure such that the antimicrobial agent is substantially incorporated throughout the surface and thickness of said structure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05967

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :B32B 27/06, 27/30, 27/36, 27/40; C08K 3/10

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 264/523, 540; 427/230, 384; 428/423.1, 480, 483, 522, 907; 523/122

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DERWENT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,869,073 A (SAWAN et al) 09 February 1999, abstract, col. 6, lines 61-66, col. 8, lines 15-35.	1, 7-10, 12, 13 --- 6, 14-16
A	US 5,614,568 A (MAWATARI et al) 25 March 1997, see abstract.	2-5, 17
A	US 5,102,657 A (REI et al) 07 April 1992, see abstract.	1, 6-16
A	US 4,895,877 A (REI et al) 23 January 1990, see abstract.	1, 6-16
X - Y	DERWENT 1997-208089, abstract of JP 09057923 A, 04 March 1997.	1-4, 7-10 --- 17

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search 04 JUNE 2000	Date of mailing of the international search report 20 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RAMSEY ZACHARIA Telephone No. (703) 305-0503

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/05967

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	DERWENT 1997-187730, abstract of JP 09048094 A, 18 February 1997.	1, 7-9, 12 ---------- 6, 10, 11, 13-16

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

264/523, 540; 427/230, 384; 428/423.1, 480, 483, 522, 907; 523/122